CELL ADHESION-INHIBITING ANTIINFLAMMATORY AND IMMUNE-SUPPRESSIVE COMPOUNDS

This application is a continuation-in-part of Application Serial Number 09/541,795, filed March 31, 2000, which is a continuation-in-part of Application Serial Number 09/474,517, filed December 29, 1999, which is a continuation-in-part of provisional Application Serial Number 60/114,097, filed December 29, 1998.

Technical Field

The present invention relates to compounds that are useful for treating inflammatory and immune diseases and cerebral vasospasm, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune response or ischemia-reperfusion injury in a mammal.

Background

Inflammation results from a cascade of events that includes vasodilation accompanied by increased vascular permeability and exudation of fluid and plasma proteins. This disruption of vascular integrity precedes or coincides with an infiltration of inflammatory cells. Inflammatory mediators generated at the site of the initial lesion serve to recruit inflammatory cells to the site of injury. These mediators (chemokines such as IL-8, MCP-1, MIP-1, and RANTES, complement fragments and lipid mediators) have chemotactic activity for leukocytes and attract the inflammatory cells to the inflamed lesion. These chemotactic mediators which cause circulating leukocytes to localize at the site of inflammation require the cells to cross the vascular endothelium at a precise location. This leukocyte recruitment is accomplished by a process called cell adhesion.

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue (Springer, T.A., 1994, "Traffic Signals for Lymphocyte Recirculation and Leukocyte Emigration: The Multistep Paradigm", Cell 76: 301-314; Lawrence, M. B., and Springer, T. A., 1991, "Leukocytes Roll on a Selectin at Physiologic Flow Rates: Distinction from and